



Dock No.: 263361US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

GROUP: 1623

Andrea CAPOCCHI

SERIAL NO: 10/516,945

EXAMINER: M.C. HENRY

FILED: August 23, 2005

FOR: A PROCESS FOR THE PREPARATION OF PIROXICAM: B-CYCLODEXTRIN INCLUSION COMPOUNDS

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS  
ALEXANDRIA, VIRGINIA 22313

Sir:

Now comes SCAPPATONE GIUSEPPE who  
deposes and states that:

1. I am a graduate of BIOLOGICAL SCIENCES and  
received my \_\_\_\_\_ degree in the year 1995
2. I have been employed by INTERNATIONAL CHEMICAL INDUSTRY  
SpA (ICI) for 32 years as a R&D DIRECTOR  
in the field of CHEMICAL MANUFACTURING

3. The following experiments were carried out by me or under my direct supervision and control.

4. About 50 liters of water was poured into a tank and heated up to a temperature of 70-73°C.

5. 8.6 kg (7.57 moles) of  $\beta$ -cyclodextrin, 1 kg (3.02 moles) of piroxicam and 1 kg of 28% ammonium hydroxide were added in succession, and the mixture was stirred for 30 min. The hot solution was poured through the tap on the temperature-controlled shelves of a freeze-dryer pre-cooled at -20°C.

6. By applying said temperature to the shelves, the solution reached the critical freezing temperature of  $-10^{\circ}\text{C}$  in 120 min, and hence at a cooling rate of about  $0.7^{\circ}\text{C}/\text{min}$ -- i.e., lower than  $1^{\circ}\text{C}/\text{min}$  as claimed in the above-identified application.

7. Under these conditions of cooling, it was observed that, when the solution reached the temperature of  $50-55^{\circ}\text{C}$ ,  $\beta$ -cyclodextrin began to re-crystallize causing de-complexation of piroxicam.

8. When the temperature reached a value lower than the eutectic temperature of the product ( $-18^{\circ}\text{C}$ ), the frozen solution containing crystalline  $\beta$ -cyclodextrin was dried under vacuum.

9. The obtained product was analyzed by differential scanning calorimetry (DSC) analysis. The thermal trace showed an endothermal melting peak at  $190-200^{\circ}\text{C}$  typical of crystalline "uncomplexed" piroxicam. A rough estimation of the area of the peak indicates the presence of at least 20-30% of crystalline piroxicam, confirming that the yield of the process is lower compared to the process claimed in the above-identified application, which specifies completeness of the inclusion reaction.

10. Therefore, pre-cooling the shelves of the freeze-dryer to a temperature of  $-20^{\circ}\text{C}$  is not sufficient for achieving a cooling rate equal to or higher than  $1^{\circ}\text{C}/\text{min}$ , and hence for obtaining a product characterized by: i) completeness of the inclusion reaction; and ii) complete amorphization, and wherein piroxicam is present in the zwitter-ionic form, as claimed in the above-identified application.

11. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of this application or any patent issuing thereon.

12. Further deponent saith not.

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(OSMMN 05/06)

Stephen J. Puffe  
Signature

APRIL 12/06/08  
Date